

Does One Voriconazole Breakpoint Suit All *Candida* Species?

Non-species-dependent interpretative breakpoints for voriconazole and *Candida* species were proposed by the Antifungal Susceptibility Subcommittee of the Clinical and Laboratory Standards Institute in January 2005 (susceptible, ≤ 1 $\mu\text{g/ml}$; susceptible dose dependent [SDD], 1 to 2 $\mu\text{g/ml}$; and resistant, ≥ 4 $\mu\text{g/ml}$) (11). The proposed breakpoints were based on the MIC distribution profile, pharmacokinetic and pharmacodynamic parameters, and the relationship between in vitro activity and clinical outcome in six phase III studies. A clinical success of 65% (binomial range, 55 to 74%) was predicted with a breakpoint of ≤ 1 $\mu\text{g/ml}$. We are concerned that a 65% target for successful therapy is too modest, especially with the overall better results seen with the echinocandins and liposomal amphotericin B in large, recently completed studies (75 to 80% response rates) (7, 9, 12).

Included in the phase III clinical studies were 1,630 cases of infection caused by the following species: *Candida albicans*, 54%; *C. tropicalis*, 15% (both MIC₉₀s, 0.25 $\mu\text{g/ml}$); *C. parapsilosis*, 11% (MIC₉₀, 0.06 $\mu\text{g/ml}$); *C. krusei*, 3% (MIC₉₀, 1 $\mu\text{g/ml}$); and finally, *C. glabrata*, 17% (MIC₉₀, 4 $\mu\text{g/ml}$). Thus, the vast majority of cases caused by isolates defined as susceptible were cases of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* infection, with MICs 4 to 5 logs below the suggested breakpoint, and those not fully susceptible were isolates from *C. glabrata* and, to a minor extent, *C. krusei* infections. As the authors point out, the infecting species was also important in determining the outcome, along with the MIC. This raises the question about whether different breakpoints are needed for different species.

C. glabrata, which was an uncommon pathogen before the introduction of fluconazole, lacks the capability to form pseudohyphae and has in some animal experiments been shown to be less virulent than *C. albicans* and *C. tropicalis* (1). In later clinical studies, *C. glabrata* has been associated with a higher mortality than other *Candida* species (4, 14); however, the possibility cannot be ruled out that a higher age and the fact that many patients initially receive fluconazole, which has inferior activity against *C. glabrata*, and not the greater virulence of the organism itself, could explain this higher mortality (2, 6, 10, 13).

We therefore question if a non-species-dependent breakpoint for voriconazole susceptibility of ≤ 1 $\mu\text{g/ml}$ is appropriate. We certainly feel that a resistance breakpoint of ≥ 4 $\mu\text{g/ml}$ is too high, as clinical response rates are inadequate. Until further experience is achieved for such isolates, we recommend the use of microbiological cutoff values for *C. albicans* and other species for which the voriconazole MICs for wild-type isolates are very low.

We are also not comfortable with the terminology “susceptible dose dependent” for voriconazole. This antifungal agent has non-linear kinetics, and reporting SDD to clinicians invites dose escalation. An argument can be made for the therapeutic drug monitoring of voriconazole in any case, partly because low-dose drug exposure may predict clinical failure and partly because high-dose drug exposure may lead to additional toxicity, as clearly demonstrated with respect to liver function tests, and possibly for other clinical manifestations (3, 5, 8). Simple dose escalation on the basis of an MIC in the SDD range and a lack of clinical response could lead to toxicity, when a switch of therapies would be most appropriate.

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Authors' Reply

We appreciate the thoughtful comments of our colleagues Arendrup and Denning regarding the breakpoints for *Candida* and voriconazole proposed in our paper (1). Indeed, we struggled with these same issues. The rationale and support for the breakpoints proposed are clearly outlined in the paper and include consideration of the MIC distribution for *Candida* and voriconazole derived using CLSI broth microdilution methods, the mechanisms of resistance to voriconazole and other azoles, pharmacokinetic and pharmacodynamic considerations, the relationship of MICs to clinical outcomes in both primary and salvage therapy trials of invasive candidiasis, and finally, the relationship between the MICs and disk zone diameters. As stated in the article, we did in fact consider alternative (lower) breakpoints than the one proposed for the susceptible breakpoint. Clearly both 0.25 and 0.5 $\mu\text{g/ml}$ would work for most species of *Candida*; however, both of those breakpoints would bisect the population of MICs obtained for both *C. glabrata* and *C. krusei*. We wished to avoid that situation and did not see the necessity for "species-specific" breakpoints. It should be pointed out that in the very seriously ill patient population represented by these clinical trials, the response rate was much lower than ideal (e.g., $\sim 80\%$). A resistance breakpoint of 4 $\mu\text{g/ml}$ represents a concentration that cannot be safely sustained and also encompasses isolates of *C. glabrata* that are resistant to fluconazole and other azoles, a phenotype that is consistent with the expression of known resistance mechanisms. Such a phenotype is not represented among isolates for which voriconazole MICs are $\leq 2 \mu\text{g/ml}$.

Separately, Arendrup and Denning comment on the differences in response rates in studies of voriconazole versus other drugs and suggest that this should drive different breakpoints. Such comparisons must be made carefully—differences in study populations, endpoint definitions, and endpoint timing reduce the ability to make simple contrasts among these studies.

Regarding the use of the term "susceptible dose dependent," we wanted to emphasize that drug exposure becomes increasingly important as MICs increase. We agree that the nonlinear pharmacokinetics of voriconazole is an issue and would support the determination of drug levels in the event of a suboptimal response to what should be an adequate dose. We believe that the phrase "susceptible dose dependent," while imperfect, conveys more clearly this message than "I," an ab-

breivation that can be taken to mean intermediate or indeterminate.

Finally, Arendrup and Denning suggest the use of microbiologic cutoff values for *C. albicans* and other species for which the voriconazole MICs are quite low. We disagree and believe that wild-type microbiologic cutoffs have epidemiologic value but less-certain clinical value, except perhaps when isolates from a patient with persistent infection are being monitored while on therapy irrespective of the actual MIC value. Clinical cutoffs should focus on clinical outcomes. At this point, it is not at all clear that an isolate of *C. albicans* for which the voriconazole MIC is even as much as eightfold higher than the wild-type microbiologic cutoff of 0.06 (encompasses 99% of all *C. albicans* isolates) (i.e., 0.5 $\mu\text{g/ml}$) would not respond clinically to standard doses of voriconazole. Labeling such isolates inappropriately as resistant may drive the needless use of intravenous therapies. The establishment of clinical interpretive breakpoints does not preclude the use of MIC distributions in the manner suggested by Arendrup and Denning. Finally, it should be noted that the CLSI breakpoint process is a dynamic one that allows for continuous evaluation and revision should compelling new data arise.

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